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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,299	10/15/2001	Kevin P. Baker	P2630P1C3	4234

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EXAMINER	
TURNER, SHARON L	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,299	BAKER ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2-10-05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1-26-05, 12-30-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

1. The amendment with unexecuted declaration filed 12-30-04 and executed declaration dated 2-10-05 have been entered into the record and have been fully considered. Applicant's executed declaration is noted to be persuasive to overcome the Furness and Tang references. In particular, the declaration evidences at least as of April 15, 1998, prior disclosure of the noted sequences of SEQ ID NO: 329 and 330, the subject of the claims. This determination is deemed to be consistent with that noted in In re Stempel and In re Moore argued by Applicants in their response of 12-30-04.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

3. As a result of Applicant's amendment, all rejections not reiterated herein have been withdrawn.

Priority

4. Applicant's traversal of 12-30-04 notes that applicants rely on disclosure of the glucose/FFA uptake assay as disclosed in PCT/US00/04341 filed 2-18-00 for utility.

In response, Applicant's disclosure of the sequence and assay as noted at p. 355-356 are found within the 2-18-00 priority document. Accordingly, the effective priority date is that of 2-18-00.

Claim Rejections - 35 USC § 101 and § 112

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 58-70 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Claims 58-70 are directed to the protein of SEQ ID NO:330, identified as PRO195, see also Figure 132. However, the protein lacks a specific and substantial asserted utility, or a well established utility, as determined according to the current Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday, January 5, 2001.

The claims are directed to isolated polypeptides having at least 80% sequence identity, with or without its signal peptide, and to the extracellular domain with or without its signal peptide. Dependent claims are directed to chimeric (containing heterologous sequences) peptides and to such peptides with an epitope tag or Fc region of an immunoglobulin. The specification contains numerous asserted utilities for the polypeptides and encoding nucleic acids, for example at pages 190-199, including use as hybridization probes, in chromosome and gene mapping, in the generation of anti-sense RNA and DNA, to identify molecules that bind to PRO (including agonists and antagonists), to make "knock-out" mice or other animals, in gene therapy, as molecular weight markers, therapeutic agents, and for the production of antibodies. The utilities that pertain solely to these nucleic acids (e.g. hybridization, chromosome and gene mapping, anti-sense) do not convey to the claimed proteins. With respect to the remaining utilities, none of these asserted utilities is specific for the disclosed PRO195 protein, as each of the aforementioned utilities could be asserted for any naturally

occurring protein, and further, as none of the asserted utilities requires any feature or activity that is specific to the disclosed PRO195 molecule.

The amino acid domains of the putative PRO195 peptide are shown in Figure 132 of the specification. In particular, the peptide is noted to contain a signal peptide at amino acids 1-31, a transmembrane domain at amino acids 241-260 and an N-glycosylation site at amino acids 90-93. However there is no description of extracellular sequences or regions of the peptide.

The specification teaches at p. 361 that the PRO195 molecule tested positive in the Rat dorsal root ganglia neuronal survival inhibition assay. However, it is noted that the cultures used in this assay are of a mixed population derived from embryonic tissue. The specification alleges that the PRO polypeptides testing positive in this assay are expected to be useful for the therapeutic treatment of neuropathic conditions associated with undesirable proliferation such as neuroblastoma, glioma or glioblastoma. Yet a search of the literature fails to reveal such correlation and there are no known exemplifications where this assay has been shown to correlate with therapeutic benefit for such diseases, see in particular Memberg et al., Mol. Cell Neurosci., 1995 Vol. 6, No. 4:323-35 and Lewis et al., J. Neurosci., 1999 Oct. 15, 19(20):8945-53. Thus, the assay fails to provide specific and substantial or well established utility.

The specification also teaches that the PRO195 molecule tested positive in the stimulation of heart neonatal hypertrophy assay and showed activity in enhancement of heart neonatal hypertropy induced by F2a as disclosed at pp. 348-349 of the specification. Polypeptides testing positive in these assays are supposedly useful for

the therapeutic treatment of various cardiac insufficiency disorders. However, the artisan recognizes multiple heart deficiency disorders. Yet the art fails to recognize treatment of any particular heart disorder with compounds testing positive in this assay. The art recognizes multiple signal transduction pathways that regulate hearty myocyte cell growth (including hypertrophy) and gene expression, see in particular Takahashi et al., Advances in Exp. Med. & Biol., 1998, 442:129-35, Jans et al., Mol. & Cell. Biochem., Jan. 1998, 178(1-2):229-36, Oi et al., Eur. J. of Pharm., 376:139-48, 1999 and Takahashi et al., J. of Cardiovas. Pharm., 1997 Dec., 30(6):725-30. Yet the art fails to recognize therapeutic uses for any particular cardiac disease with peptide compounds that stimulate hypertrophy. In contrast, it would appear that compounds inhibiting such stimulation would be candidates in treating cardiac hypertropy. Accordingly, this assay does not establish specific and substantial asserted utility or well established utility for PRO195 or other peptides testing positive as disclosed.

Significant further research is required of the skilled artisan to determine the function and use of the PRO195 molecule. Thus, for the aforementioned reasons, the specification fails to denote a specific and substantial asserted utility or a well established utility for the claimed polypeptides of the invention.

Applicants traverse in the 12-30-04 response that utility is provided via the glucose/FFA uptake assay in that PRO195 inhibited uptake to .5 that of the insulin control. Applicnats argue that evidence that increasing glucose uptake is a hallmark of therapeutic agents such as troglitazone and poigliazone amongst others as noted and

that accordingly the artisan would accept agents that increase glucose free fatty acid uptake as indicative of therapeutic agents.

Applicants arguments filed 12-30-04 have been fully considered but are not persuasive. In particular PRO195 was found to inhibit glucose/free fatty acid uptake. (The assay is not noted to be distinguished as to whether the inhibition is amongst glucose and/or free fatty acid uptake). The references argued by Applicants and all reasoning for utility based thereon is upon that of an increase. In contrast PRO195 was found to inhibit glucose/free fatty acid uptake. No evidence is offered as to how an inhibitor in such an assay should be used. As noted above, it would be contrary that such inhibitory compounds would be therapeutically beneficial in treating any specific disease. Notably, inhibition of glucose free fatty acid uptake is contrary to and works in the opposite direction to therapeutics related to insulin resistance and/or diabetes. Thus, the references and evidence via the cited references fails to note specific and substantial utility that is either asserted or well established and recognized in the art based upon uptake .5 that of insulin. Accordingly, rejection is maintained.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 58-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification describes peptide sequence consisting of SEQ ID NO:330, which is shown to test positive in the assays noted above. However, the claims as written include polypeptides having at least 80-99% sequence identity with SEQ ID NO:330 and polypeptides including or lacking various regions including; lacking its signal peptide, the extracellular domain, the extracellular domain but lacking its signal peptide, but for which no particular biological activity or function is recited. Thus, the claims are directed to various genus' defined solely by homology and comparison.

However, the instant disclosure of a single polypeptide, that of SEQ ID NO:330 with the instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by

describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus.

However, the instant specification discloses only the single sequence and no other members of the claimed genus. Given the unpredictability of homology comparisons, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000 and the fact that the specification fails to provide objective evidence of any additional sequences with the same requisite function, it cannot be established that a representative number of species have been disclosed to support the genus claim. No

activity is set forth for the additional sequences and there is no evidence for a correlation or nexus provided between possession of any homologous feature and the activities as noted such that it is clearly conveyed that possession of any polypeptide having such structural similarity would possess the same function. Thus, the claims lack adequate written description support.

Applicants argue in the 12-30-04 that the claim amendments and guidance obviate the invention in that the noted effects may be suitably tested.

Applicant's arguments filed 12-30-04 have been fully considered but are not persuasive. As noted above, the art fails to recognize noted use and/or any structure and/or function relationship amongst molecules that inhibit glucose or free fatty acid uptake. (The assay is not noted to be distinguished as to whether the inhibition is of glucose and/or free fatty acid uptake). Further the specification provides only a single sequence which provides for such inhibition and fails to describe what other sequences inhibit. Moreover, there is no description or guidance as to how similar the other related sequence need to be such that the variability in structure correlates to inhibition or some other known and useful function. Accordingly, the single species member with no disclosed structural and functional correlation is insufficient to describe the genus of molecules as instantly claimed via % homology language. Accordingly, rejection is maintained.

6. In addition to the aforementioned defects with respect to 112, first paragraph as noted above, the following deficiencies are noted even should utility be found.

7. Claims 58-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the variable peptide sequences and for such generic sequences where no requisite functional activity is provided as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. For example, Jobling et al, Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of conserved structural components to both biological function and immunological recognition.

Instant specification discloses a single PRO195 sequence that differs from the other sequences disclosed. The specification notes that the peptide exhibits activity in

the noted DRG neuronal survival inhibition assay, in the stimulation of heart neonatal hvpertrophv and activity in enhancement of heart neonatal hypertropy induced bv F2a. However, the specification further fails to note such conserved activities in any 80-99% variable molecule. However, applicants claims are directed to peptides with 80-99% homology, to extracellular domains and to sequences lacking the signal peptide where no requisite function is required.

The specification does not enable this broad scope of the claims that encompasses a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that the polypeptides retain sufficient structural similarity to evoke activity. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful and the skilled artisan would not necessarily expect functional conservation among homologous sequences. Moreover, no similar function is required of the additional sequences. The artisan would be unable to determine how to use such similar sequences that lack common function. The additional members would require further experimentation to discover their requisite use. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation

left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

Thus, in view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims the artisan cannot make and use the invention without undue experimentation.

Applicants similarly argue in the 12-30-04 response that the claim amendments and inhibition within the glucose/free fatty acid uptake assay enable the claims.

Applicant's arguments filed 12-30-04 have been fully considered but are not persuasive. As noted above, the art fails to recognize noted use and/or a structure function relationship amongst molecules that inhibit glucose free fatty acid uptake. Further the specification provides only a single sequence which provides for such inhibition and fails to describe what other sequences inhibit and/or how those sequences or structures correlate to some known and useful function or effect such that the single species member may describe a genus. Moreover, the art fails to recognize noted benefit via testing positive for inhibition in such an assay. Accordingly, the single sequence exhibiting inhibition fails to evidence enablement for the artisan to make and use the invention commensurate in scope with the claims when the use or benefit to the disclosed or any related sequence is not provided. There is no reasonable expectation that the % identical sequences share the same function, and moreover as set forth above, no utility is noted for the related molecules based upon testing positive for inhibiting glucose and/or free fatty acid uptake. Therefore, rejection is maintained.

Status of Claims

7. No claims are allowed.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

Sharon L. Turner, Ph.D.
April 4, 2005

SHARON TURNER, PH.D.
PRIMARY EXAMINER

3-31-05